REMARKS

The Office Action and the Advisory Action have been carefully reviewed. Claims 93, 95 and 98-120 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

In the Advisory Action of December 14, 2006, the examiner indicated that the previous amendment of 10/26/06 overcame the lack of enablement and the lack of written description rejections.

Regarding the sole outstanding rejection, the rejection under 35 U.S.C. §103(a) as being unpatentable over Nakamura et al., applicants' have further amended the claims to distinguish over Nakamura. Claims 93 and 118 are amended to further define IGIF/IL-18 as mainly showing a single protein band with an activity of inducing interferon-claims 93 and 118 are amended to further define IGIF/IL-18 as mainly showing a single protein band with an activity of inducing interferon-γ production at a position corresponding to 19,000 ± 5,000 daltons when electrophoresed in a sodium dodecyl sulfate (SDS) polyacrylamide gel free of reducing agent, as supported in the present specification at page 23, Experiment 2-1. Claim 120 is amended to further define IGIF/IL-18 as an antigen that has been extracted and collected from the liver of a mouse previously challenged with *Corynebacterium parvum*, as supported in the present specification at pages 21-23, Experiment 1.

Applicants' further comments are as follows below.

As applicants have pointed out repeatedly, the IGIF/IL-18 recited in the present claims should be distinguished from the factor disclosed in Nakamura in its origin, its molecular weight, activity and IFN-gamma inducing activity as summarized in the Table below. Please note that this same Table was presented at page 10 of the amendment dated May 8, 2006, except that a typographical error under Nakamura's factor is corrected here so as to correctly indicate that Nakamura's factor "loses" its activity when treated with SDS-PAGE.

	IGIF of Okamura reference	"factor" of Nakamura reference
origin	liver of mouse	serum of mouse
molecular weight	19,000 ± 5,000 Da (SDS-PAGE)	50,000 ~ 55,000 Da (SDS-PAGE)
activity	will not lose its activity when treated with SDS-PAGE	will lose its activity when treated with SDS-PAGE

Nevertheless, the examiner still alleges that the post filing date Okamura reference confirms that IGIF in the serum sample (75 kDa in Nakamura, *Infect. Immun.* 61:64-70, 1993) was proved to be the same IGIF as that found in the liver extract (19 kDa). Applicants respectfully disagree with the examiner.

Claims 93 and 118 have been amended to define IGIF/IL-18 as mainly showing a single protein band with an activity of inducing interferon-γ production at a position corresponding to 19,000 ± 5,000 daltons when electrophoresed in a sodium dodecylsulfate (SDS) polyacrylamide gel free of reducing agent. In other words, IGIF/IL-18 recited in the present claims show its activity of inducing IFN-gamma

production at a position corresponding to 19,000 ± 5,000 daltons on SDS-PAGE even in the absence of a reducing agent (free of a reducing agent).

By contrast, Okamura reports that a protein having a molecular weight of 19,000 ± 5,000 that is derived from Nakamura's factor does not show the activity of inducing IFN-gamma production in the absence of a reducing agent. Please see page 3969, left column, lines 12-17, where Okamura teaches:

> As shown in Fig. 5a, an IFN-gamma-inducing activity was observed in the protein species with a molecular mass of 19 kDa beside the 75- to 80 kDa protein by molecular sieving with Superdex 75 in the presence of dithiothreitol (DTT). On the other hand, the activity was observed only in the molecular species of 75 to 80 kDa without DTT.

Please also see Fig. 5b at page 3970 of Okamura, where it is shown that the molecular species of 19 kDa does not show its activity in the absence of the DTT reducing agent.

In this regard, applicants believe that IGIF/IL-18 recited in the present claims is distinguished from the 19 kDa molecular species derived from Nakamura. Therefore, applicants submit that the IGIF/IL-18 recited in the present claims is distinguished from the factor disclosed in Nakamura, even if Nakamura's factor comprises the molecular species of 19 kDa disclosed in the Okamura reference.

Attached hereto is a copy of "The Cytokine Handbook" second edition, edited by Angus W. Thomson, pp.23-224, 1994, where it is taught:

> Monoclonal antibodies specific for mouse 1L-10 revealed that, as for many other cytokines, some IL-10 molecules appear to be nonfunctional and

> antigenically different, since two monoclonal antibodies were isolated that bound IL-10 but did not recognize any biologically active molecules (Mosmann et al., 1990).

This teaching from a reference text can be taken to imply to one of ordinary skill in the art that the molecular species of 19 kDa derived from Nakamura's factor may be different from the IGIF/IL-18 recited in the present claims in its antigenicity. In light of this implication, one of ordinary skill in the art would likely consider that the molecular species of 19 kDa derived from Nakamura's factor may not have been effective in obtaining a monoclonal antibody which recognizes IGIF/IL-18.

Furthermore, both Nakamura and Okamura do not disclose that they actually obtained monoclonal antibodies which recognize IGIF even though they indicate the necessity of such monoclonal antibodies. This therefore suggests that the presently claimed invention would not have been obvious over Nakamura to one of ordinary skill in the art.

In response to applicants' previous argument that it would have been difficult to obtain monoclonal antibodies which recognize IGIF based on the disclosure of Nakamura because Nakamura did not have a sufficient amount of IGIF to obtain the monoclonal antibodies, the examiner alleges that IGIF producing cells would overcome the difficulty due to the lack of IGIF. Applicants also respectfully disagree with the examiner on this issue. Nakamura discloses at page 69, left column, lines 13-14 that "The cells producing the factor have also <u>not</u> been identified." Okamura also discloses at page 3972, left column, line 1 that "The cellular origin of IGIF remains <u>unknown</u>."

Accordingly, claims 93 and 118, and claims dependent therefrom would not have been obvious over Nakamura to one of ordinary skill in the art.

Claim 120 defines an isolated antibody obtainable by using, as an antigen, IGIF/IL-18 that has been extracted and collected from the liver of a mouse previously challenged with *Corynebacterium parvum*. Nakamura's factor was obtained from mouse serum, and not from the liver of mouse. Applicants therefore believe that Nakamura does not make obvious claim 120.

Reconsideration and withdrawal of the §103(a) obviousness rejection over Nakamura are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By /ACY/
Allen C. Yun
Registration No. 37,971

ACY:pp
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\S\SUMA\okamura2b\Pto\2007-02-22amendment.doc